CLAIMS:

1. A method for generating a non-human mammalian model of an autoimmune disorder, said method comprising the steps of:

(a) producing intermated progeny of a first and a second transgenic non-human mammal of the same species, wherein said first mammal expresses a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) and said second mammal expresses a selected peptide that binds to said TCR, which selected peptide is selectively expressed by MHC class II positive antigen presenting cells (APC) of said second mammal; and

(b) selecting from said progeny those mammals that co-express said TCR and said selected peptide,

wherein said selected progeny develop an autoimmune disorder.

2. The method according to claim 1, wherein said model is a high penetrance model of said disorder and wherein said selected peptide is a naturally-occurring, recombinant or synthetic MHC class II-restricted T cell determinant that specifically binds with high affinity to said TCR.

3. The method according to claim 2, wherein at least 50% of said progeny before selection develop said autoimmune disorder.

4. The method according to claim 2, wherein said TCR is the TS1 TCR and said determinant is A/PR/8 hemagglutinin (HA) peptide S1.

5. The method according to claim 4, wherein said first mammal is a transgenic mouse that expresses MHC class II-restricted TCR with high affinity for an A/PR/8 hemagglutinin (HA) peptide S1 and said second mammal is a transgenic mouse that expresses DNA encoding the influenza A/PR/8 HA peptide S1 operably linked to a functional fragment of the MHC class II I-Eα promoter.

6. The method according to claim 1, wherein said model is a low penetrance model of said disorder and wherein said selected peptide is a naturally-occurring, recombinant or synthetic protein or peptide fragment that binds with low affinity to said TCR.

7. The method according to claim 6, wherein less than 25% of said progeny before selection develop said autoimmune disorder.

8. The method according to claim 6, wherein said TCR is the TS1(SW) TCR and said peptide is A/PR/8 hemagglutinin (HA) peptide S1.

9. The method according to claim 8, wherein said first mammal is a transgenic mouse that expresses a MHC class II-restricted TCR with high affinity for an synthetic mutant S1 analog of A/PR/8 HA, but with low affinity for the native A/PR/8 HA S1 peptide; and wherein said second mammal is a transgenic mouse that expresses DNA encoding the native influenza A/PR/8 HA S1 peptide operably linked to a functional fragment of the MHC class II I-Eα promoter.

10. The method according to claim 9, wherein said mutant analog is an HA peptide SEQ ID NO: 2 differing by two amino acids from said A/PR/8 HA S1 peptide SEQ ID NO: 1.

11. The method according to claim 1, wherein in said second mammal a first nucleic acid sequence encoding said selected peptide is operably linked to a second nucleic acid sequence that directs expression of said first nucleic acid sequence selectively to MHC class II positive cells.

12. The method according to claim 11, wherein said second nucleic acid sequence encodes the MHC class II I-E□ gene promoter, non-MHC class II sequences involved in expression of the invariant chain, non-MHC class II H2-M promoter, the Dec205 promoter and the Cd11c promoter.

13. The method according to claim 1, wherein said mammal is a mouse.

14. The method according to claim 1, wherein said autoimmune disorder is inflammatory arthritis.

15. The method according to claim 14, wherein said disorder is characterized by inflamed joints with bone resorption, mononuclear cell infiltrates and pannus formation.

16. The method according to claim 15, wherein said reaction further comprises at least one of a symptom selected from the group consisting of bone erosion, bone remodeling, vasculitis, interstitial pneumonitis in the lung, anti-nuclear antibodies in serum, and weight loss.

17. A non-human mammalian model of an autoimmune disorder, produced by the method of claim 1.

18. A non-human mammalian model of an autoimmune disorder having a high penetrance genotype, produced by the method of claim 2.

19. A non-human mammalian model of an autoimmune disorder having a low penetrance genotype, produced by the method of claim 6.

20. A transgenic non-human mammal that expresses a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) and expresses a selected peptide that binds to said TCR, which selected peptide is selectively expressed by MHC class II positive antigen presenting cells (APC), wherein said mammal develops the phenotypic symptoms of an autoimmune disorder.

21. The transgenic mammal according to claim 21, wherein all germ cells and somatic cells of said mammal contain at least one transgene comprising a first nucleic acid sequence that encodes a major histocompatibility (MHC) class II-

restricted T cell receptor (TCR) operably linked to regulatory sequences directing its expression; and a second nucleic acid sequence that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive antigen presenting cells (APC).

22. The transgenic non-human mammal according to claim 21, wherein the phenotype is conferred by at least one transgene contained in somatic and germ cells of said mammal which directs said co-expression of said selected peptide selectively by its APC and said TCR.

23. The transgenic non-human mammal according to claim 20, wherein the autoimmune disorder is inflammatory arthritis.

24. The transgenic mammal according to claim 20, wherein said selected peptide is a naturally-occurring, recombinant or synthetic MHC class II-restricted T cell determinant that specifically binds with high affinity to said TCR, and wherein said mammal exhibits high penetrance of said disorder.

25. The transgenic mammal according to claim 20, wherein said selected peptide is a naturally-occurring, recombinant or synthetic protein or peptide fragment that binds with low affinity to said TCR, and wherein said mammal exhibits low penetrance of said disorder.

26. A recombinant mammalian cell containing at least one transgene comprising a first nucleic acid sequence that encodes a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) operably linked to regulatory sequences directing its expression; and a second nucleic acid sequence that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive antigen presenting cells (APC).

27. The cell according to claim 26, wherein said TCR is the TS1 TCR and said peptide is the influenza A/PR/8 hemagglutinin (HA) peptide S1.

28. The cell according to claim 26, wherein said TCR is the TS1(SW) TCR and said peptide is the influenza A/PR/8 hemagglutinin (HA) peptide S1.

29. A method for producing a transgenic non-human mammalian model of an autoimmune disorder, said method comprising introducing at least one transgene comprising a first nucleic acid sequence that encodes a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) operably linked to regulatory sequences directing its expression; and a second nucleic acid sequence that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive antigen presenting cells (APC) into a fertilized egg, wherein said egg is transplanted into a pseudopregnant mammal and developed to term, and wherein said at least one transgenic offspring contains said transgene and is bred to form a transgenic mammal having said autoimmune disorder.

30. A method for producing a transgenic non-human mammalian model of an autoimmune disorder, said method comprising the step of

(a) introducing at least one transgene comprising a first nucleic acid sequence that encodes a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) operably linked to regulatory sequences directing its expression; and a second nucleic acid sequence that encodes a selected peptide that binds to said TCR, operably linked to a sequence that directs expression of said selected peptide selectively to MHC class II positive antigen presenting cells (APC) into an embryonic cell of a mammal, wherein said cell is injected into an embryo of said mammal, said embryo is transplanted into a pseudopregnant mammal and allowed to develop to term;

(b) identifying at least one transgenic offspring containing said transgene; and

(c) breeding said offspring to form a transgenic mammal having said autoimmune disorder.

31. The method according to claim 29 or 30, wherein said selected peptide is a MHC class II-restricted T cell determinant that specifically binds with high affinity to said TCR, and wherein said transgenic mammal exhibits high penetrance of said disorder.

32. The method according to claim 29 or 30, wherein said selected peptide binds with low affinity to said TCR, and wherein said transgenic mammal exhibits low penetrance of said disorder.

33. A cell culture comprising cells derived from tissues of a transgenic non-human mammal of any of claims 20 to 25.

34. A method of screening a compound for the ability to effect symptoms of an autoimmune disorder, comprising the steps of:

(a) administering a test compound to a mammalian model of autoimmune disorder selected from the mammal of any of claims 17 to 25; and

(b) comparing the severity of said symptom in the mammalian model (a) to a control mammal to which said test compound was administered.

35. The method according to claim 34, wherein said disorder is autoimmune inflammatory arthritis.

36. A method of identifying a gene product responsible for the development of autoimmune disorders comprising the steps of:

identifying expression levels of a gene product of a mammalian model of autoimmune disorder selected from the mammal of any of claims 17 to 25;

comparing expression of said gene product with the expression of the same or analogous gene product in a control mammal; and

determining a difference in the expression of said gene product, wherein the absence, upregulation or downregulation of said gene product between said model and said control.

37. The method according to claim 36, wherein said disorder is autoimmune inflammatory arthritis.

38. The method according to claim 36, wherein said control mammal is sibling of said model, which sibling does not demonstrate any or all of the symptoms of said autoimmune disorder.

39. A method for identifying a biochemical marker of an autoimmune disorder comprising:

comparing the T cells or MHC class II positive APC of a mammalian model with a high genotypic penetrance of said disorder with the T cell of a mammalian model with a low genotypic penetrance of said disorder; and

identifying a biochemical marker present on T cells or MHC class II positive APC of one model that is not present the T cells or MHC class II positive APC of the other model;

wherein the presence of said marker on said high penetrance model and absent on said low penetrance model or the absence of said marker on said high penetrance model and its presence on said low penetrance model is an indicator of a high likelihood of the development of said autoimmune disorder.

40. The method according to claim 39, wherein said high penetrance model is a non-human mammalian model of an autoimmune disorder of any of claims 18 or 23.

41. The method according to claim 44, wherein said high penetrance model is a transgenic non-human mammal that expresses a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) and expresses a naturally-occurring, recombinant or synthetic MHC class II-restricted T cell determinant that specifically

binds with high affinity to said TCR, which selected peptide is selectively expressed by MHC class II positive antigen presenting cells (APC), or a direct progeny thereof.

42. The method according to claim 39, wherein said low penetrance model is a non-human mammalian model of an autoimmune disorder of any of claims 20 or 24.

43. The method according to claim 42, wherein said low penetrance model is a transgenic non-human mammal that expresses a major histocompatibility (MHC) class II-restricted T cell receptor (TCR) and that expresses by its MHC class II positive antigen presenting cells (APC) a naturally-occurring, recombinant or synthetic protein or peptide fragment that binds with low affinity to said TCR, or the direct progeny thereof.

44. The method according to claim 39, wherein said disorder is autoimmune inflammatory arthritis.

45. A novel composition for the diagnosis or treatment of inflammatory arthritis isolated by use of the mammalian model of claim 1.